

1

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## 2-BROMO- $\alpha$ -ERGOCRYPTINE

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Claims priority, application Switzerland, May 31, 1968, 8,168/68

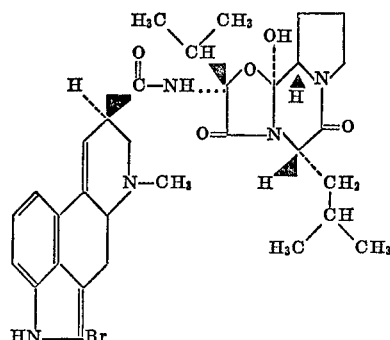
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2 Claims

### ABSTRACT OF THE DISCLOSURE

The invention concerns 2-bromo- $\alpha$ -ergocryptine of the formula

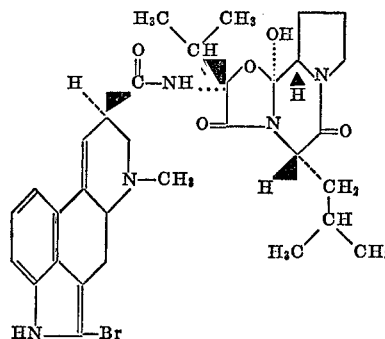


and pharmaceutically acceptable acid addition salts thereof.

The compounds are useful in inhibiting lactation, i.e. they inhibit the secretion of luteotropic hormone and furthermore exhibit antifertility properties.

This is a continuation-in-part of application Ser. No. 827,144, filed May 23, 1969, now abandoned.

The present invention relates to 2-bromo- $\alpha$ -ergocryptine of Formula I,



and acid addition salts thereof.

2-bromo- $\alpha$ -ergocryptine and its acid addition salts may be obtained in accordance with the invention by brominating ergocryptine in a solvent, which is inert under the reaction conditions, with a mild brominating agent, e.g. N-bromophthalimide, N-bromosuccinimide or N-bromocaprolactam, purifying the resulting 2-bromo- $\alpha$ -ergocryptine in manner known per se and then optionally converting it into its acid addition salts.

Suitable brominating agents are amides or imides, brominated on the nitrogen atom, of aliphatic or aromatic carboxylic or sulphonic acids, e.g. N-bromophthalimide, N-bromosuccinimide or N-bromocapro-

2

lactam (1 to 3 mols) or a bromo-dioxane complex (0.5 mol Br<sub>2</sub>).

Bromination is conveniently effected in an inert, polar solvent, e.g. dioxane, acetonitrile or methylene chloride, at a temperature between 10 and 80° C.

Purification of the resulting crude 2-bromo- $\alpha$ -ergocryptine may be effected in conventional manner, e.g. by chromatography and/or recrystallization.

2-bromo- $\alpha$ -ergocryptine is a crystalline substance at room temperature and forms stable salts, which are crystalline at room temperature, with organic or inorganic acids. Examples of acids which may be used for salt formation are inorganic acids, such as hydrochloric, hydrobromic or sulphuric acid, or organic acids, such as oxalic, tartaric or methanesulphonic acid.

2-bromo- $\alpha$ -ergocryptine and its pharmaceutically acceptable acid addition salts inhibit the secretion of luteotropic hormone (prolactin) and are useful because of their antifertility properties, which differ from similar representatives of the ergotoxine group, e.g.  $\alpha$ -ergocryptine or ergocornine, in that

- (1) their effect is more specific, and
- (2) they are better tolerated.

2-bromo- $\alpha$ -ergocryptine and its pharmaceutically acceptable acid addition salts exhibit the above-mentioned properties at daily dosages ranging from about 0.6 milligram to about 2.5 milligrams per kilogram animal body weight. However, for larger mammals, suitable daily doses range from about 2 to about 20 mg., in view of the specificity of action.

The properties of 2-bromo- $\alpha$ -ergocryptine indicated above may be ascertained as follows:

#### (1) Antifertility effect

Each of two fertile female rats (control and test animal) is placed with an experienced male rat in a cage for a period of 19 days. The test preparation or pure solvent is injected subcutaneously to the female rats on the 5th, 10th and 15th day of the test. During the autopsy on the 19th day the uterine horns are examined under a magnifying glass for implantations and resorptions. Each dose group consists of 11 test animals and the same number of control animals. Evaluation of the test is effected by making the fertility of the test animals equivalent to 100% and expressing the fertility decrease of the test animals as a percentage. These tests are repeated with different doses in order to ascertain the relationship between dose and effect and to determine an ED<sub>50</sub>.

Table I gives a summary of the results of such a test series. An ED<sub>50</sub> of 0.75 mg./kg. may be calculated from the fertility inhibition values in accordance with the test method of Litchfield and Wilcoxon, J. Pharmacol. 96, 99 (1949).

TABLE I

Dose, mg./kg.	Anti-fertility effect, percent	Number of fetus for every pregnant animal		Number of resorptions	
		V	K	V	K
0.25	0	10.3	10.3	5	8
0.5	0	10.9	11.3	8	10
0.65	40	11.2	10.4	4	8
0.75	50	12.2	9.3	0	9
0.85	55	11.6	11.3	11	6
1.0	80	12.0	10.7	3	9
1.25	91	12.0	10.6	1	4
2.5	100	-----	10.9	0	3
20.0	100	-----	11.2	0	9

NOTE.—V=Test animals; K=Control animals.

#### (2) Determination of the specificity of the antifertility effect

In what follows the quantitative ratios of implantation inhibition and lactation inhibition of 2-bromo- $\alpha$ -ergo-